Preventing End-Stage Renal Disease

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Interest in evidence-based medicine is increasing greatly, with the focus on treatment that prevents organ failure and that may prolong life. Type 1 and Type 2 diabetes are conditions associated with increased mortality, mainly as a result of renal and cardiovascular diseases, and blindness. All three complications usually occur together. In recent years, more focus has been placed on treating patients early to prevent future organ damage. Microalbuminuria is an important intermediary end-point that correlates strongly with future advanced renal disease, retinopathy and mortality. Several trials have studied patients with microalbuminuria and also patients in more advanced stages of the disease who have proteinuria (termed overt nephropathy). Recent evidence indicates that achieving optimal glycaemic control reduces the risk of an increase in urinary albumin excretion before the development of microalbuminuria. Angiotensin-converting enzyme (ACE) inhibitors are effective in reducing microalbuminuria, partly independent of their blood pressure reducing effects. In Type 1 and Type 2 diabetic patients with microalbuminuria, long-term treatment with ACE inhibitors (7–8 years) prevents the predicted decrease in glomerular filtration rate (GFR); optimal glycaemic control is also important in preventing the decline in GFR. This is important because GFR is usually well preserved in Type 1 and Type 2 diabetic patients with microalbuminuria and a predicted decline in GFR can therefore be prevented. In overt renal disease, studies that focused mostly on Type 1 diabetic patients have shown that the rate of decline in GFR can be reduced. Long-term studies in Type 1 diabetic patients have also demonstrated that mortality caused by end-stage renal disease can be postponed. Mortality associated with cardiovascular diseases, e.g. myocardial infarction, is reduced more effectively in diabetic patients treated with ACE inhibitors and beta-blockers than in non-diabetic patients treated with the same drugs. Screening for microalbuminuria, the attainment of optimal glycaemic control, and early treatment with ACE inhibitors and other antihypertensive drugs are necessary to prevent progression of diabetic complications, especially diabetic nephropathy. However, there is some controversy about the initial use of calcium channel blockers. In conclusion, early achievement of improved glycaemic control is the most important factor in the prevention of diabetic complications. Antihypertensive treatment is clearly also important.

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Introduction

Detection of microalbuminuria is fundamental in the diagnosis of early renal disease, especially in diabetes but also in essential hypertension.[1] Microalbuminuria predicts mortality (especially in Type 2 diabetes)[2] and morbidity, in diabetes, and also in the general population where it is associated with abnormalities characteristic of the so-called metabolic syndrome or 'Syndrome X', i.e. hypertension, dyslipidaemia, glucose intolerance, obesity and coronary heart disease. Ferranini proposed that microalbuminuria should be included as a component of the metabolic syndrome because a clustering of these abnormalities occurs in individuals with microalbuminuria.[3] Microalbuminuria is often present at the time of clinical diagnosis in Type 2 diabetes.[4]

Microalbuminuria is usually defined as an excretion rate of albumin between 30–300 mg·day^{-1} or 20–200 μg·min^{-1} or a urinary albumin-to-creatinine ratio of 3–30 μg·mg^{-1}. An excretion rate below 30 mg·day^{-1} is designated 'normoalbuminuria' and above 300 mg·day^{-1} as 'clinical proteinuria' or 'macroalbuminuria'.[5] However, it should be emphasized that these criteria are, to some extent, chosen arbitrarily, because the parameter is a continuous variable in diabetic and non-diabetic populations. Furthermore, an excretion rate in the upper normal range is predictive of disease progression[6,7] and later development of complications, as well as mortality in the general population.[8]

Professional organizations, such as the American Diabetes Association,[9] have proposed that regular screening for microalbuminuria should be carried out to identify at-risk patients who should be monitored more meticulously. Patients with microalbuminuria should be treated intensively, particularly with respect to glycaemic control and antihypertensive treatment. Patients with microalbuminuria usually have well preserved renal

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function, and diabetic patients may even have glomerular hyperfiltration,[10,11] which is associated with poor glycaemic control.[5] When identifying patients with microalbuminuria, intensified treatment can be initiated before any important decline in renal function has occurred. However, patients with microalbuminuria have more advanced structural damage[12,13] and are characterized by a number of abnormalities as well as risk factors, as indicated above. Therefore, it would be beneficial to identify at-risk patients before they develop microalbuminuria, e.g. those patients with poor metabolic control, modest elevation of blood pressure, glomerular hyperfiltration and elevated albumin excretion rate.

The overall prevalence of diabetic nephropathy was approximately 35 % in Type 1 and Type 2 diabetes, but results from a study in Sweden by Bojestig *et al.*, suggest that the incidence of nephropathy is declining, as evidenced by only a small number of Type 1 diabetic patients developing nephropathy in their study cohort.[14] However, this observation from Sweden could not be confirmed by the group at the Steno Hospital in Copenhagen.[15] The reason for the decline in diabetic nephropathy is not clear but the so-called 'natural history' may be modified considerably by more intensive intervention throughout the course of Type 1 and Type 2 diabetes.[16] This relates to metabolic control and blood pressure as major factors but other issues are of importance, e.g. smoking. In addition, ethnic origin is an important factor in determining the risk of nephropathy. Diabetic nephropathy is more commonly seen in African Americans with Type 2 diabetes, and results from new studies of the Pima Indians (unpublished data) suggest that, with long-term follow up, practically all Type 2 diabetic patients within that group will develop renal disease. These patients are usually in poor glycaemic control. This information is important because it has been suggested that there may be more important susceptibility factors that could relate to genetics.[17] Comparison has been made with diabetic retinopathy where almost all patients ultimately develop lesions. However, important distinctions occur because renal disease is judged usually by proteinuria, not biopsies. In fact, the cumulative incidence of diabetic retinopathy and nephropathy may be almost identical if histological or ophthalmological examinations are used. Another point under discussion is why some patients fail to develop diabetic nephropathy despite poor glycaemic control. A possible explanation for this is that two factors must be present in combination to produce important clinical disease, i.e. high blood pressure and high blood glucose. When these factors are present in a patient, clinical experience indicates that nearly all patients will develop clinically relevant nephropathy and retinopathy.

New studies emphasize the role of good metabolic control in advanced nephropathy in Type 1 diabetes, as has been documented by Breyer *et al.*,[18] and more recently by Mulec *et al.*[19] These results are in concert with information from the Steno Diabetes Centre, London and also from Gothenburg.[20–22] Clearly, in advanced nephropathy, elevated blood pressure is of importance and the combination of factors in overt nephropathy may lead to marked differences in progression; this also applies to Type 2 diabetes.[23] With poor control of glycaemia and blood pressure, the fall rate is high (approximately 8 $ml \cdot min^{-1} \cdot year^{-1}$), but with efficient control this rate may reach 1–2 $ml \cdot min^{-1} \cdot month^{-1}$ (personal communication, H-H. Parving). Obviously, obtaining perfect metabolic control in all patients is not possible, especially in those patients who have developed nephropathy already or who are at risk of doing so, because the underlying factor for development of complications is poor glycaemic control, which may not be easy to rectify even after those complications have occurred. This is exemplified in a study from the UK, the Microalbuminuria Collaborative Study.[24]

The concept of 'natural history' may be wrong unless used specifically in patients who have poor glycaemic control. However, if risk factors such as hyperglycaemia and blood pressure elevation can be controlled, few patients with Type 1 and Type 2 diabetes may actually develop proteinuria, and eventually end-stage renal disease. Furthermore, with advanced nepthropathy, glycaemic control appears to be of great importance in Type 2 diabetes.[25]

Such a strategy requires considerable resources, not only from the healthcare providers but also from patients. It is of interest that low socio-economic class is an important risk factor, as shown in new studies carried out in Germany (personal communication, Ingrid Mülhaüser). This may partly explain difficulties in obtaining sufficiently good glycaemic control. It may be easier to implement treatment with angiotensin-converting enzyme (ACE) inhibitors, even in the normo-albuminuric state as proposed recently by Ravid *et al.*[26] However, both strategies should be exercised within the clinical setting, as discussed below.

Results from a controlled study by Pedersen *et al.*, showed that in patients with Type 1 diabetes and normal albumin excretion rate, the ACE inhibitor enalapril reduces the filtration fraction and the albumin excretion rate within the so-called normal range, showing that ACE inhibition leads to desirable changes in renal function, which may be protective in the long term.[27]

Most studies have been conducted in Type 1 or Type 2 diabetic patients with microalbuminuria; when untreated, they will develop progressive microalbuminuria followed by a decline in glomerular filtration rate (GFR). Many studies[1,9,28–31] have shown consistently that ACE inhibition can reduce microalbuminuria, which suggests a reduction in intraglomerular pressure. Since patients with albuminuria usually have well preserved renal function, long-term studies are needed to document preservation of GFR. Results from two controlled studies, one in Type 1 diabetes[32] and the other in Type 2 diabetes,[28] have shown that preservation of GFR occurred in patients treated with ACE inhibitors followed up for

7–8 years. Therefore, it is highly likely that intervention with ACE inhibitors imparts a renoprotective effect with renal function being preserved over many years. New studies have shown preservation of normoalbuminuria when patients are treated at this stage.[26] Controversy exists over the use of calcium channel blockers.[33]

This is also consistent with findings in overt renal disease in Type 1 diabetic patients, where several studies have shown that treatment with ACE inhibitors reduces the proteinuria and the decline in GFR,[29] and demonstrated that the more dramatic the effect on proteinuria, the more the effect on GFR preservation. The level of blood pressure is clearly important and some studies suggest that any treatment that results in normotension under all circumstances will, to some extent, preserve GFR in diabetes over many years. In Type 2 diabetes, the rate of decline in GFR is correlated with blood pressure as in Type 1 diabetes, but it is not feasible ethically to carry out trials without effective antihypertensive treatment in such patients. Studies currently in progress are investigating overt renal disease in Type 2 diabetic patients who use angiotensin II receptor antagonists, but results will not be available until 2002–2003. Meanwhile, clinical judgement, partly extrapolating from Type 1 diabetes, must be employed when treating proteinuric patients with Type 2 diabetes.

In both types of diabetes, it is increasingly clear that strict glycaemic control and effective antihypertensive treatment are the main components in preserving renal and retinal function in these patients.[9,28,31,34,35] Interestingly, blood pressure levels also relate to retinopathy in normoalbuminuric Type 1 diabetic patients.[36]

UKPDS and Effects of Treatment

New results from the United Kingdom Prospective Diabetes Study (UKPDS) focus also on blood pressure control and blood glucose control.[37–41] The complexity of diabetes, especially of Type 2 diabetes, is becoming increasingly clear. From the time it is diagnosed, Type 2 diabetes is characterized not only by hyperglycaemia, often with impaired insulin secretion, but also by blood pressure elevation and dyslipidaemia. It is partially related to obesity and insulin resistance, not to mention genetic factors. The abnormalities tend to worsen with time, which may make intention-to-treat analysis somewhat less sensitive. More than three decades ago Harry Keen pinpointed two key risk factors in diabetes—high blood glucose levels and high blood pressure—both associated with microalbuminuria. The UKPDS has recently extended the number of risk factors to include dyslipidaemia and smoking.[42] However, due to the complexity of the disease and the slow but progressive development of complications over years and decades, strongly substantiated intervention strategies against diabetic complications have been largely missing in Type 2 diabetes. Early on in the UKPDS, researchers became aware that blood pressure elevation, as we originally observed in diabetic renal disease,[43] may be an even stronger risk factor for Type 2 diabetes, and they therefore included blood pressure treatment in the study.

A vigorous blood glucose policy reduces the risk of diabetes-related complications in Type 2 diabetes, in the same way that sulphonylurea and insulin therapies reduce the risk of microvascular complications. The risk of myocardial infarctions also tends to be reduced. A key finding is that there appears to be no specific adverse cardiovascular outcomes with the two different regimens. The beneficial effect includes metformin which, regarding end-points, is quite effective in obese patients, but it remains to be explained why it works less well in combination therapy. Thus, the 'glucose toxicity hypothesis' in Type 2 diabetes is confirmed in line with the Diabetes Control and Complications Trial (DCCT), and controversy should end now.[44] It can still be presumed that diet and exercise work, because these were part of all patients' regimens, but we do not know about end-points or the effectiveness of other types of new oral anti-diabetic agent. However, insulin should probably be used more and more to control glycaemia.

The UKPDS shows that tight control of blood pressure strongly reduces the risk for complications in diabetes. This risk reduction is more convincing than with tight blood glucose control, where the difference between the treatment regimens with respect to HbA_{1c} was probably not large enough (7.0 % vs. 7.9 %) to document marked differences in cardiovascular outcome. Long-term tight blood pressure control in hypertensive Type 2 diabetic patients results in a significant reduction in any diabetes-related end-points, including diabetes-related deaths. All causes of mortality failed to reach statistical significance, but important effects were seen in the typical diabetic microvascular complications including diabetic eye diseases. Cardiovascular complications such as heart failure and stroke, as in essential hypertension,[45] were strongly reduced, and some effect on myocardial infarctions was noted. Early treatment, as in this study, is important even with certain normotensive microalbuminuric patients.[46] This is a new concept in the treatment strategy of all diabetic patients.[46] In my opinion, combining strict metabolic and blood pressure control should give an even better outcome, and it does not surprise me that not only is antihypertensive treatment more effective, but also the results happen more quickly. Late treatment in proteinuric Type 2 diabetes is difficult, but new strategies are being developed.

ACE inhibitors and beta-blockers were shown to have no specific advantages or disadvantages. However, larger and longer-term trials may be needed to incorporate the effects on very distant end-points such as progressive nephropathy and end-stage renal disease. In the literature there are arguments for the use of both classes of drugs in diabetes, but the UKPDS suggests that blood pressure reduction *per se* may be more important than the therapy used, at least when comparing these two types of drugs with looser control. The well-known side-effects were

noted for both classes of agents, but the ACE inhibition was better tolerated by most patients, with fewer side-effects. Health economist analyses showed that a tight blood pressure control is cost-effective when compared with other widely used preventive strategies, and is more feasible for most clinicians and patients than tight blood glucose control. Importantly, combination drug strategies are often needed, as in many other newer trials, making evaluation of single drugs increasingly difficult. The important calcium-channel blocker controversy has not yet been settled,[47] but further information should become available from the UKPDS.

The Type 2 diabetic patients described in the UKPDS are quite typical, but interestingly their definition of diabetes at the onset of the study appears to have been in accordance with standards of today.[48] Patients with a fasting plasma glucose level higher than 6.0 mmol·l^{-1} were included, whereas a level of fasting plasma glucose between 6.1 and 6.9 mmol·l^{-1} is now designated 'impaired fasting glucose'. According to new criteria, a repeated fasting plasma glucose above 7.0 mmol·l^{-1} is used for diagnosis of diabetes. However, it should be noted that at that stage patients were on a diet.

Results of small trials with positive outcomes on microvascular disease have been, or are soon to be, published.[49] A series of recent antihypertensive trials (including many Type 2 diabetic patients) has been published with similar results. These include the Systolic Hypertension in the Elderly Program (SHEP) study (low doses of diuretic-based beta-blocker and reserpine),[50] the Hypertension Optimal Treatment (HOT) trial (calcium-channel blockers, with various combinations)[51] and the SYST-EUR Study (calcium-channel blockers with ACE inhibitors and diuretics as reserves).[52] The Captopril Prevention Project (CAPP) favoured ACE inhibitors over conventional treatment in Type 2 diabetes;[53] while the Appropriate Blood Pressure Control in Diabetes (ABCD) study showed larger reduction in non-fatal myocardial infarction with ACE inhibitors compared with calcium-channel blockers in hypertensive diabetes and resulted in controversy.[47] No J-shaped curves were noted in any of the studies. In the UKPDS, mean blood pressure of the intensified group was reduced to 144/82—a reduction of 10 mmHg in systolic and 5 mmHg in diastolic blood pressure, which is comparable with the other studies, except the HOT study in which blood pressure was reduced further. In the HOT study, diastolic blood pressure reduction ranged from 20 to 24 mmHg. The actual goal in the clinical management is probably a level around 140/85, or even lower, as in essential hypertensive trials[45] because the correlation between blood pressure and cardiovascular disease is likely to be curvilinear with no threshold. The goal for HbA_{1c} levels is 7 % or lower, taking into account the entire condition of the patient. As in the DCCT, any reduction of a high level of HbA_{1c} is important.

Type 2 diabetes risk factors also include dyslipidaemia, and the Scandinavian Simvastatin Survival Study (4S) showed that secondary intervention in diabetic patients is quite effective.[54] In the UKPDS, primary intervention is now in progress, a quite important area for further research, as are effective anti-smoking campaigns in diabetes. Thus an intensified multifactorial intervention strategy, possibly including aspirin treatment, seems warranted.[55]

Conclusions

Screening for microalbuminuria, the attainment of optimal glycaemic control and early treatment with ACE inhibitors are necessary to prevent progression of diabetic complications, especially diabetic nephropathy. Improved glycaemic control from the earliest stages of the disease is the most important factor in the prevention of diabetic complications; later, blood pressure control becomes important. Consequently, treatment against both risk factors is essential to prevent renal and cardiovascular disease in Type 1 and Type 2 diabetes.[54]

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